Global Smokeless Tobacco Research Agenda

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Executive Summary

Smokeless tobacco (ST) is defined as any tobacco product that is not burned when used. ST may be used alone or in combination with other substances. ST may be used at any site and by any means that permits the absorption into the human body of nicotine and other constituents that are in tobacco, on tobacco, or added to tobacco.

ST has not been studied nearly as well as has tobacco products that are burned when used. Much of what is known about ST is about patterns of use. However, in most countries even within that subject, large knowledge gaps exist. Although ST use is classified as a human carcinogen by the International Agency for Research on Cancer (IARC),[i] and since 2000, the United States National Toxicology Program,[ii] there are many gaps in our understanding of its effects on other chronic diseases such as cardiovascular disease and diabetes.[iii] It is clear however, that the use of ST is widespread globally. Tobacco products are extremely varied and are often used in combination with other ingredients such as areca nut, an animal carcinogen according to the IARC.[i] The purpose of developing a Global Smokeless Tobacco Research Agenda (GSTRA) is to help investigators and organizations that fund research be aware of the many types of ST research needed. The agenda should help promote investigation into diverse research questions so that eventually, balanced and timely, evidence-based information becomes available to individuals and public policy decisionmakers everywhere. The key premise is that public, administrative and personal beliefs, policies, and actions related to the use of ST should be, to the extent they are knowable, based upon facts.

The GSTRA outline is divided into seven research subject areas: (Type I) ST production research, (Type II) ST consumption research, (Type III) ST-associated health effects research, (Type IV) research on influences on ST consumption, (Type V) research on interventions to prevent ST use or for cessation, (Type VI) health policy research, and (Type VII) research systems issues. With regard to Type III, the World Health Organization's (WHO) definition of "health" is used to encourage systematic inquiry into all ways that people, individually and collectively, might be affected by ST use. With regard to Type IV, "influences" encompass industry use-promoting and public health use-suppressing methods and influences at the social system, individual, and biological levels.

The GSTRA is intended to be a framework within which every important ST-related issue can be placed. It is meant to help funding organizations establish research priorities so that issues that are most timely, of highest importance, or least understood are examined first, most carefully, and most extensively. Various criteria for guiding priority setting are proposed. The GSTRA should be in a dynamic state so that research questions and priorities can change as the store of human knowledge grows and world affairs change.

Introduction

All tobacco forms are addictive and cause harm. ST can condition the brain for other chemical dependencies. Youths commonly use multiple forms of tobacco while their tobacco dependence develops. Tobacco products used by adults often vary over time according to determinants such as product affordability, risk-perception, changing customs, and other social conditions.

Addressing the many unexplored and under-investigated research questions is likely to provide important information for the development of sound public perceptions, public policy, and public health programs. Two international ST conferences in 1991 and 2000 reported on the state-of-the-science. In addition to these reports, several speakers at the 2002 3rd International Conference on Smokeless Tobacco (3rd ICST) identified several research questions that remain open. One conference conclusion was that the

development of a global research agenda should be a high-priority component of a long-range plan for reducing ST use and dependence and its adverse health consequences.

Public, administrative and personal beliefs, policies, and actions related to the use of ST should be, to the extent they are knowable, based upon facts.

Major scientifically established facts about the oral use of ST is that it

1. represents a significant health risk.
2. is not a safe substitute for smoking cigarettes.
3. can cause cancer and a number of noncancerous oral conditions.
4. can lead to nicotine addiction and tobacco dependence.[iv]

In developing this research agenda, it was assumed that

1. the best means to protect individual and public health from tobacco harms is to achieve abstinence, prevent initiation, and prevent relapse.
2. a comprehensive and authoritative global tobacco control program, with harm reduction as one component, is necessary to minimize adverse effects of tobacco.

These assumptions are derived from precepts stated in the 2001 Institute of Medicine report, *Clearing the Smoke*. [v]

Global ST Research Agenda Development Process

Most studies that focus on ST or include a ST component have been investigator-initiated. While this process has advanced the science, it does not ensure the systematic investigation of important issues. Consequently, speakers at the 3rd ICST were asked, in addition to summarizing the state-of-the-science, to identify significant research questions. Their recommendations, and others subsequently identified, are organized into general subject areas. These experts were asked to review and comment on the drafts and their comments were incorporated in the final draft. It is anticipated that the draft global research agenda will facilitate systematic research progress in understanding the burden of morbidity and mortality from ST use and identify successful approaches to ameliorating these consequences. It should be refined over time through a dynamic review among investigators, research-funding organizations, and potential users of research.

ST Definition

Smokeless tobacco (ST) is defined as any tobacco product that is not burned when used. ST may be used alone or in combination with other substances. ST may be used at any site and by any means that permits the absorption into the human body of nicotine and other constituents that are in tobacco, on tobacco, or added to tobacco. However, most ST products are used orally. The National Cancer Institute and the Centers for Disease Control and Prevention prepared a compendium of fact sheets on smokeless tobacco products specifically for the participants of the 3rd ICST. The fact sheets include information about the brand and common names of the products, their geographic location of use, their constituents (ingredients), how the products are used, who primarily uses the products, and the processes for manufacturing the products.[vi]

The term, “smokeless tobacco” or “ST” is consistent with the World Health Organization’s definition in the Framework Convention on Tobacco Control (i.e., “ ‘tobacco products’ means products entirely or partly made of the leaf tobacco as raw material which are manufactured to be used for smoking, sucking, chewing or snuffing.’ ”)[vii] The term excludes products that are intended to be smoked, but includes products not intended to be burned, even when tobacco is not the primary ingredient.

ST Global Agenda: Framework for Specific Research Content Areas

Type I: Smokeless Tobacco Production Research

The primary focus of a Type I investigation is to understand the nature and management of ST up to, but not including, end-user handling and use, and the effect of these factors on human exposure and biological dose (amount of toxicants in the body of the users) of these products in humans.

A. ST-related agriculture

B. ST processing and manufacturing

C. ST finished products:
1. Traditional ST products by description/-type, common names, places, and ways used
2. Industry-manufactured ST products by description/-type, common names, places, and ways used
3. Novel ST products and devices (e.g., dentifrices, cosmetics)
4. Chemistry and constituents of different ST products
    a. Nicotine delivery effectiveness by product design
    b. Additives (e.g., chemicals that enhance nicotine effects)
    c. ST combined with other psychoactive drugs placed in or taken together with ST (e.g., alcohol, opium)
    d. ST combined with foods and/or beverages
    e. ST contaminants, organic and inorganic (e.g., fungi, herbicide-pesticide-fungicide residues, fertilizer constituents)
    f. Changes in ST chemistry in storage and use (e.g., fermentation, other chemical reactions)

D. ST distribution systems and storage

Type II: Smokeless Tobacco Consumption Research – Use by Populations

The primary focus of a Type II investigation is to understand ST-related behavior by individuals and in defined populations to identify populations at high risk of adopting particular ST behaviors, for targeting intervention efforts; for assessing trends in use effects of broad social, legal, economic, and public health trends on use of ST; and for estimating burden of disease in populations.

A. Prevalence of use by ST type and brands within type:
1. Applications (e.g., dermal, nasal, oral, gastric, other mucosal contact)
2. Frequency and duration of use
3. Product types
4. Changes in product preferences over time
5. Other descriptors of individual behavior

B. Prevalence of ST specific product use by various population descriptors:
1. Biological descriptors (e.g., age – including youths and elderly, gender – including pregnant women, race, other genetic characteristics)
2. Geographic descriptors (e.g., globally, by WHO-defined region, by country, by geographic subdivisions within country)
3. Sociological descriptors (e.g., ethnicity; cultural group – including ceremonial uses, family-work-recreation network subgroups; politically defined groups – including migrants, displaced groups; economic-based groups – including by formal education and other experience-based factors such as SES, dominant social environment effects on recent immigrants)
4. Time descriptors (e.g., prevalence trends in ST use by year)

5. Relationship to non-ST tobacco use behaviors (e.g., smoking, smoking intensity, first product used, mixed-multiple product use, switching, progression patterns, ST types in multiple product tobacco use)
6. Prevalence of extent of exposure to ST
    a. Frequency of use
    b. Time usually kept in mouth
    c. Amounts used
    d. Distribution of user classifications in the population (e.g., never user, current user, former user, regular user)

C. Prevalence of ST use in relation to behaviors other than tobacco use (e.g., tobacco-free behavior, risk-taking, hygiene, other drug use/abuse and/or drug dependencies)

D. Other ST-related consumption research

Type III: ST-Associated Health Effects Research

The primary focus of a Type III investigation is to understand ST-related health outcomes. Positive and negative outcomes are defined as advantages and disadvantages to the physical, mental, and social well-being of users and society resulting from use. Type III studies include specific effects, associations, and underlying mechanisms for each ST product, combination of ST products, and ST products contrasted to burned tobacco products. The following conditions have been identified in at least one study as being potentially related to ST use.[viii]

A. Physical health effects research:
1. Molecular, cellular, and central nervous system (CNS) changes among ST users and their offspring (e.g., comparative brain structure functions among smoking, ST, and abstainers; chemical modifiers; short- and long-term recovery mechanisms)
2. Morbidity and mortality (e.g., prevalence, incidence, relative risk, micro-dynamics, other)
    a. Cardiovascular system: blood pressure, angina, heart attack, hypertension, arrhythmia, sudden death, vasospastic disorders
    b. Reproductive outcomes (e.g., gestation period; stillbirths; sudden infant death syndrome; birth weight; fetal nicotine addiction; fetal exposure in relationship to long-term deficits in behavioral, cognitive, and emotional states; other outcomes)
    c. Neoplasms:
        (1) at site of ST contact (oral, nasal, other mucosa, dermal)
        (2) distal/systemic (e.g. other mutagenesis and carcinogenisis descriptors and mechanisms)
    d. Oral effects other than neoplasms (e.g., periodontal and oral mucosal changes, links between oral and major systemic diseases, other)
    e. Effects on Diabetes, type II, and other metabolic disorders
    f. Effects on the immune system
    g. Effects on wound healing
    h. Other system effects
3. Morbidity and mortality cofactors (e.g., viruses, nutrition)
4. Effects of ST use on non-tobacco drug therapies (e.g., drug interactions)
5. ST physical-related safety and risks associated with each ST product defined (e.g., Are there safety thresholds for toxic substances in ST?)

B. Mental health effects research:
1. ST dependence: initiation, graduation, dependence, cessation, relapse, abstinence
2. ST dependence relative to the use of non-ST tobacco products (e.g., ST as a gateway or inhibitor)
3. ST dependence and concurrent or alternative use of smoking tobacco
4. ST dependence and co-substance dependencies (e.g., alcohol, other psychoactive drug use)
5. ST dependence and psychiatric co-morbidities (e.g., depression and other mood effects)

6. Maternal ST exposure and fetal brain development, child behavior, and human development
7. ST psychologically related safety and risks associated with each product defined
8. Other ST-related mental health effects

Note: The term "dependence" is chosen to highlight changes in CNS function, hormone balance, neuromuscular, sympathetic, and other systems and integration of repetitive, compulsive behaviors and where attempts to be abstinent create transient and/or long-term mental disorders.

C. Social health effects research:
1. ST use association with other social markers (e.g., education, peers, risk behaviors)
2. ST use and economic issues (e.g., costs to consumer, family, taxpayer, other economic)
3. ST use and social system issues (e.g., legal, public area hygiene and esthetics/litter)
4. Other ST-related social impact

Type IV: Research on Influences on ST Consumption

The primary focus of a Type IV investigation is to understand those forces that influence the consumption of ST and the biological dose of ST constituents in the user's body. Some are external to the user, while others, such as genetic factors, are intrinsic to the user. Actions that are identified as effective in promoting ST use should be met with comparable (legal and ethical) responses that discourage use. Research is needed to ensure that such information and measures are scientifically accurate, feasible, and culturally acceptable.

A. Social influences on knowledge, perceptions, attitudes, and ST use – positive and negative:
1. Parental, peer, and other direct informant knowledge, attitude, and behavior
2. Cultural and religious influences (i.e., individual identification with cultural setting including hospitality [e.g., betel use] or ceremonial use)
3. Media and communications influences by social norms and other theories – Effectiveness of marketing and counter-marketing approach used
    a. by type (e.g., advertising and promotion, industry and public health marketing strategies)
    b. by content
    c. by channel (e.g., product labeling, messengers including the entertainment industry, promotional items, public service announcements, other means to convey messages)
    d. Health claims (e.g., diversions from health issues, claims that products are "safe" or "safer")
    e. Health consequences (e.g., cancer)
    f. Use of science (e.g., how media presents science)
    g. Source credentials
4. Preventive measure effectiveness, cost-benefits (e.g., school-based, community-based, and other organizations)
5. Non-public health-based social system interventions (e.g. religious, civic, human rights, environmental, other community-based, country, and global organizations)

B. Personal factors:
1. Individual user's and abstainer's knowledge, perceptions, and attitudes (e.g., of related benefits and risks)
2. Terms used to describe ST in general, product types, products on perceptions, attitudes, and behavior
3. Influence of past experiences
4. Access to ST (e.g., perceptions and attitudes about free samples, availability at social events)
5. Attitudes about and involvement in other risk-taking (e.g., smoking) or health behaviors (e.g., physical activity)

C. Biological determinants of individual behavior and biological dose of ST received:

1. Susceptibility to addiction
2. Genotypes involved in addiction or metabolism of toxicants
3. Exposure to chemicals that alter cellular functions related to behavior (*in utero* and after birth)
4. Conditioning experience (e.g., early stress, abuse, nutrition, etc., affecting CNS development)
5. Anthropology and ethnology
6. Interaction with ST pH, frequency and amount used, duration of retention in mouth
7. Other biologically based determinants of behaviors

Type V: Research on Interventions to Prevent ST Use or for Cessation

This section addresses interventions designed to prevent ST use or for cessation. Research attention should focus on developing and assessing effectiveness and efficacy of approaches.

A. Cessation strategies research (individual and group):

1. Self-help approaches to cessation (e.g., "cold turkey," setting a quit date, involvement of family and friends)
2. Behavioral interventions by type of intervention (e.g., cognitive, hypnosis, emphasizing bad breath, esthetics)
3. Pharmacological interventions for cessation (e.g., prescription, over-the-counter, combined drugs, other)
4. Technology-based interventions (e.g., telephone, hot-line, computer-assisted, Web-interactive, other technology)
5. Interventions when co-dependencies present: clinical, other

B. Cultural/social variations in intervention effectiveness, cost-benefits:

1. Globally, by WHO-defined region, by country, by geographic subdivisions within country
2. By common epidemiological bio-measures (e.g., age, gender, race)
3. By sociological factors (e.g., ethnicity, cultural group, family-work-recreation subgroups, SES)
4. By special populations (e.g., migrants, pregnant women, elderly, youths, other)

C. Provider setting (e.g., private practice, hospital, managed care organizations, traditional practitioner, school, other)

D. Provider type (e.g., physician, nurse, community worker)

E. Alternative tobacco use research:

1. Impact on tobacco use initiation; in culture, trans-country (e.g., European Union policy and practice effects in South Asian populations)
2. Impact on duration and amount of ST and smoked tobacco use
3. Impact on tobacco cessation attempts and rates
4. Impact on tobacco user health
5. Impact on public perception and attitudes about tobacco use (e.g., nicotine-free claims when aren't free, warning label accuracy, effectiveness, evaluation standards)
6. Ethical assessment of issues (e.g., untested products, industry ability to lower toxins but don't)
7. Impact on public policy, regulatory systems, and other social system issues

Type VI: ST Health Policy Research

This section addresses research on the legislative processes that influence ST use.

A. Marketing policy issues:

1. Product availability and trade (e.g., youth access)
2. ST products and nicotine replacement therapies

3. Special population access to clinical and public health interventions
4. Monitoring media for how issues are framed by tobacco industry (e.g., use of science, type of media, position of media, source credentials)

B. Legal and regulatory policy research:

1. Country and subunit law development, enforcement and their effects (e.g., variable effects by age, preemption, exemption from consumer protection laws)
2. International law (e.g., WHO Framework Convention on Tobacco Control; sales and sales restrictions; licit and illicit trade; economic factors such as taxes, price elasticity, other international policy)
3. Monitoring product production, manufacturing and distribution systems (e.g., changes in products over time, shifts from/to smoking products, product development) in terms of image presented, product placement, cultural context, and other influences on perceptions and behavior
4. Other oversight mechanisms
5. Law enforcement (e.g., relative efficiency and effectiveness of ST to other tobacco-related laws, regulations, and policies)
6. Special marketing and regulatory issues related to the use of traditional tobacco products
7. ST-related economic research
    a. Pricing policies (e.g., demand elasticity)
    b. Tobacco-related behavior by relationship between smoked and smokeless tobacco prices
    c. Economic interventions
    d. Other micro- and macro-economic ST-related research
8. Transnational impact of local/regional policies and practices (i.e., beyond policy area -- see special case, European Union policy in non-EU countries, IV-D-2)

C. Monitoring the toxicants and addictive chemicals in tobacco products' addictive and toxic profile, and user trends in how the ST products are used/consumed

Type VII: Research Systems Issues

The primary focus of a Type V investigation is to understand, assess, and improve the research systems available to address ST research questions (i.e., the knowledge, attitudes, beliefs, expectations, and methods of assessing the need for investigation, funding and other investigation support; and evaluating research quality, disseminating research findings, and building the personnel, facilities, communication systems and other components that constitute a viable research enterprise).

A. Research systems organization:

1. Assessment systems for evaluating the strength and validity of ST studies (e.g., industry funding, quality in terms of sample size, study design, number and types of studies, meta analyses of studies)
2. Guideline development (e.g., ST guidelines, inclusion of a ST component in other tobacco or substance abuse/dependence guidelines)
3. Research infrastructure development (e.g., resource development, strategic planning, and review system monitoring and assessment)
4. Monitoring and assessing ST research (e.g., Web search, searchable databases, description of ongoing studies and communication among investigators, intervention efficaciousness)

B. Surveillance and epidemiology:

1. Global surveys: (e.g., which ST questions to include)
2. National and regional monitoring (e.g., ST type, use, and health effect status by country and districts within counties)

3. Standards (e.g., uniform definitions and basic/core survey questions and instruments, ability to aggregate data, minimum sample sizes and other guidelines)
4. Data access systems (e.g., Web sites, publications, other)

C. Public health resources (e.g., development of management systems, partnerships, and networks for organizing ST-related surveillance, communications, policies, and intervention systems)

D. Potential criteria for prioritizing ST research:

1. Geographic criteria (e.g., region and/or country with least information about ST types, uses, health effects, and influences on use and availability of research guidelines that are country- and/or culture-specific)
2. Issue criteria (e.g., identification of products used before determination of prevalence of use; before determination of causal relationships and associated health effects; before describing public knowledge, perceptions, and attitudes about use; before determining underlying factors affecting use)
3. Study design quality, research quality
4. Population criteria (e.g., largest culture first, multi-center within two or more counties and/or cultures)
5. Political and other resource issues (e.g., availability of investigators and research infrastructure, other research capacity, acceptability of the research in the populations to be studied, communications, etc.)
6. Investigator/team qualifications, collaboration capability
7. Other criteria

E. Potential organizational roles

1. Selecting criteria and prioritizing ST research
2. Creating, promoting, and respecting international standards
3. Financing ST research – global and country research goals, objectives, and parameters
    a. Governmental research organizations (e.g., international, country, education institutions, other)
    b. Non-governmental (e.g., foundations, professional organizations, other)
    c. Tobacco company research (internal, direct grants, and indirectly)
    d. Other industries and sources

F. Research-finding dissemination systems:

1. Research community – transdisciplinary
2. Health care delivery and other professional education systems
3. Health care system workers
4. Public policymakers
5. Public at large
    e. Defined subpopulations
    f. Other populations

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